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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/088,405 | 07/24/2002 | Baskaran Chandrasekar | 410718.90395 | 2963 |

7590 12/05/2006

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| EXAMINER | |
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

DATE MAILED: 12/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/088,405 | CHANDRASEKAR ET AL. | |
| | Examiner | Art Unit | |
| | Abigail M. Cotton | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-8,10-14,16-18 and 20-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10-14,16-18 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 6, 2006, has been entered.

Claims 1, 3-8, 10-14, 16-18 and 20-23 are pending in the application and are being examined on the merits herein.

The rejection of claim 1 under 35 U.S.C. 112, second paragraph, for lacking proper antecedent basis, is being withdrawn in view of Applicant's amendment to the claim.

The rejection of claims 1, 8-9, 14 and 18-19 under 35 U.S.C. 102(b) as being anticipated by Ungs is being withdrawn in view of Applicant's amendments to the claims, as Ungs does not specifically teach a method including administering 17Beta-estradiol in the does unit of from 1 to 5000 µg/Kg of patients body weight, as recited in newly amended claim 1.

The terminal disclaimer filed on October 6, 2006 disclaiming the terminal portion of any patent granted on this application that would extend beyond the expiration date of U.S. Patent Application Serial No. 10/602,934 has been reviewed and is accepted. The terminal disclaimer has been recorded. Accordingly, the provisional obviousness-type double-patenting rejection made over this application is being withdrawn.

The claims are being rejected as follows.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-4, 8, 10, 12-14, 16-18, 20 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,866,561 to Mark T. Ungs, issued February 2, 1999.

Ungs teaches a method for inducing angiogenesis in blood vessels proximal to stenosed regions, including application of an estrogen compound to the blood vessel walls at a treatment site proximal to or upstream of the stenosis (see abstract, in

particular.) Ungs teaches that restenosis following PTCA is a signification problem, and that administration of estrogen to the stenosed, dilated region after PTCA has been suggested for the purposes of preventing restenosis (see column 1, lines 10-20 and 40-52, in particular), and thus teaches administration to an injured site, i.e. one that has been injured by PTCA. Ungs teaches that it is thus desirable to increase perfusion to heart tissue in place of or in addition to PTCA treatment (see column 1, lines 54-65, in particular.) Ungs teaches that a preferred method of treating stenosis involves application with a double walled drug delivery balloon catheter, as well as by coating a stent with an estrogen compound or by puncturing a vessel wall (see column 2, lines 5-45, in particular.) Ungs teaches that preferred estrogen compounds include 17-Beta estradiol (see column 4, lines 1-12, in particular), as in claims 1 and 14. Accordingly, Ungs teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury. Ungs furthermore teaches single administration of 17-Beta estradiol, as recited in claims 8 and 18, as Ungs teaches the compound can be administered via a stent or balloon catheter.

Ungs does not specifically teach administering 17beta-estradiol in the specific dosages as recited in claims 1, 3-4 and 16-17.

However, it is noted that Ungs teaches that 17Beta-estradiol is a preferred estrogen compound (see column 4, liens 1-11, in particular), and Ungs also teaches various methods of application of the estrogen via catheters, stents, etc, and refers to

prior art catheter, for example, that are used for the local administration of drugs (see column 3, lines 1-15, in particular.) Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of 17Beta-estradiol provided in the method, according to the guidance provided by Ungs, to provide the desired treatment, such as the desired reduction in restenosis. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, claims 1, 3-4 and 16-17 are considered to be unpatentable over Ungs.

It is respectfully pointed out that the recitation "for improving reendothelization and vascular endothelial function" in claim 1 has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *in re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152 88 USPQ 478, 481 (CCPA 1951.) Furthermore, it is noted that as Ungs teaches administering the same compound via the same method as that

instantly claimed, and to reduce the incidence of restenosis following a treatment such as PTCA that induces vascular injury, it is considered that the method of Ungs would necessarily also improve reendothelization and vascular endothelial function in a patient having suffered vascular injury, as recited in the claim.

Regarding claims 12-13 and 22-23, Ungs teaches that restenosis following PTCA is a significant problem (see column 1, lines 10-20, in particular), and teaches that treatment to increase perfusion to heart tissue, such as with estrogen compounds, are desirably performed in place of, or in addition to, PTCA (see column 1, lines 50-65, in particular.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the 17-beta estradiol following or simultaneously with the PTCA, based on the teachings of Ungs, with the expectation of increasing perfusion to heart tissue and for reducing the likelihood of restenosis.

Regarding claims 10 and 20, Ungs teaches that the estrogen can be administered with an ionic carrier (pharmaceutically acceptable carrier) in an iontophoresis method using delivery balloon catheter (see column 2, lines 32-40, in particular.)

Claims 5-7, 11 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,866,561 to Mark T. Ungs, issued February 2, 1999, as applied to claims 1, 3-4, 8, 10, 12-14, 16-18, 20 and 22-23 above, and further in view of U.S. Patent No. 4,727,064 to Josef Pitha, issued February 23, 1998.

Ungs is applied as discussed above, and teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury, for example via catheter or a stent (see column 2, lines 5-45, in particular), as recited in claims 11 and 21. Ungs does not specifically teach administration of hydroxypropyl-beta-cyclodextrin (HPCD) as recited in claims 5-7. Ungs also does not specifically teach providing a pharmaceutically acceptable carrier in administering the 17-beta estradiol via stent, as recited in claims 11 and 21.

Pitha teaches that pharmaceutical preparations containing cyclodextrin derivatives have enhanced dissolution properties and thus enhanced absorption by the body (see abstract, in particular.) Pitha teaches that cyclodextrin mixtures effectively solubilize liphophilic drugs in aqueous media (pharmaceutically acceptable carrier), and have low toxicity (see column 2, lines 35-60, in particular.) Pitha demonstrates that estradiol is a drug that exhibits improved solubility in combination with hydroxypropyl-beta-cyclodextrin (see Table I, in particular.) Accordingly, Pitha teaches the benefits in improved solubility and absorption of providing estradiol in combination with hydroxypropyl-beta-cyclodextrin, and in a pharmaceutically acceptable carrier such as aqueous media, as recited in claims 11 and 21 are known.

Regarding the dosage amount recited in claim 7, Pitha teaches that the cyclodextrin additives may generally be utilized in a weight percent of from about 40-

60% of the drug solution (see column 2, lines 62-68, in particular.) Pitha furthermore teaches intraperitoneal injection of hydroxypropyl-beta-cyclodextrin into mice was non-fatal at 3.2g/kg, and teaches a lack of oral toxicity of the hydroxypropyl-beta-cyclodextrin (see column 4, line 64 through column 5, line 5, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to optimize the amount of hydroxypropyl-beta-cyclodextrin provided in the medication, according to the guidelines provided by Pitha, to provide the desired solubility and absorption characteristics of the estradiol. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the hydroxypropyl-beta-cyclodextrin and pharmaceutically acceptable carrier of Pitha in the 17-beta estradiol delivery method of Ungs, with the expectation of improving the solubility and absorption of the 17-beta estradiol compound in the patient.

***Response to Arguments***

Applicant's arguments with respect to the rejections of the claims have been considered but are moot in view of the new grounds of rejection.

In particular, Applicant's assert that Ungs does not teach administering the estradiol for improving reendothelization and vascular function, as recited in the claims, and thus does not teach the recited method.

The Examiner respectfully disagrees. Ungs teaches that restenosis following PTCA is a significant problem (see column 1, lines 15-20, in particular.) In other words, the site at which PTCA has been performed, which is necessarily a site at which injury has occurred, is the same site that is susceptible to restenosis. Ungs teaches that administration of estrogen to stenosed dilated region (i.e. the injured site) after PTCA has thus been suggested for the purposes of preventing restenosis (see column 1, lines 40-53, in particular.) While Ungs does teach that not all regions can be treated with PTCA, Ungs also teaches that it is also desirable to reduce the incidence of restenosis following PCTA or other procedures by providing the estrogen compounds (see column 1, lines 50-65, in particular.) Thus, Ungs teaches administration of the estrogen compound to a site that is susceptible to restenosis, and that has or will experience injury due to techniques such as PTCA or other invasive techniques.

Thus, as Ungs teaches administering the same compound via the same method as that instantly claimed, it is considered that the method of Ungs would necessarily also improve reendothelization and vascular endothelial function, as recited in the claim.

The declaration filed under Rule 132 on January 23, 2006 and signed by Dr. Richard Sean Stack has been fully considered but has not been found persuasive. In particular, the declaration provides statements arguing that it cannot be predicted whether an agent known to prevent or reduce smooth muscle cell proliferation and/or to prevent or reduce blood vessel wall thickening will also promote reendothelization, as recited in the claim (see point 12, in particular.) Thus, the declaration argues that the knowledge that beta-estradiol had an ability to reduce smooth muscle cell proliferation is not sufficient for someone skilled in the art, to predict that beta-estradiol could also promote re-endothelization and endothelial function (see point 14, in particular.)

These arguments are not found persuasive because, as noted above, since Ungs teaches administering the same compound via the same method steps as those instantly claimed, it is considered that the method of Ungs also necessarily improves reendothelization and vascular endothelial function. The fact that applicant has recognized another advantage which would flow naturally from following the teachings or suggestion of the prior art cannot be the basis for patentability when the prior art teaches the invention or when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

## ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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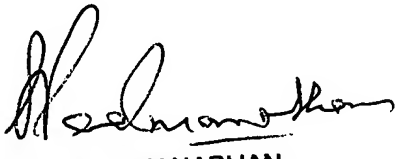

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